AD_____

Award Number: W81XWH-04-1-0773

TITLE: Multimodality Image-Guided HDR/IMRT in Prostate Cancer: Combined Molecular Targeting Using Nanoparticle MR, 3D MRSI, and 11C Acetate PET Imaging

PRINCIPAL INVESTIGATOR: Karen Kurdziel, M.D.
Michael Hagan, M.D., Ph.D.
Jeffery Williamson, Ph.D.
Donna McClish, Ph.D.
Panos Fatouros, Ph.D.
Jerry Hirsch, MSc, PharmD
Rhonda Hoyle
Kristin Schmidt
Dorin Tudor, Ph.D.
Jie Liu

CONTRACTING ORGANIZATION: Virginia Commonwealth University
Richmond, VA 23284

REPORT DATE: August 2005

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

# REPORT DOCUMENTATION PAGE

*Form Approved*
*OMB No. 0704-0188*



| 1. REPORT DATE *(DD-MM-YYYY)* | 2. REPORT TYPE | 3. DATES COVERED *(From - To)* |
|---|---|---|
| 01-08-2005 | Final | 30 Jul 04 – 29 Jul 05 |

**4. TITLE AND SUBTITLE**
Multimodality Image-Guided HDR/IMRT in Prostate Cancer: Combined Molecular Targeting Using Nanoparticle MR, 3D MRSI, and 11C Acetate PET Imaging

**5a. CONTRACT NUMBER**

**5b. GRANT NUMBER**
W81XWH-04-1-0773

**5c. PROGRAM ELEMENT NUMBER**

**6. AUTHOR(S)**
Karen Kurdziel, M.D., Michael Hagan, M.D., Ph.D., Jeffery Williamson, Ph.D., Donna McClish, Ph.D., Panos Fatouros, Ph.D., Jerry Hirsch, MSc, PharmD, Rhonda Hoyle, Kristin Schmidt, Dorin Tudor, Ph.D., Jie Liu

E-Mail: kurdziel@hsc.vcu.edu

**5d. PROJECT NUMBER**

**5e. TASK NUMBER**

**5f. WORK UNIT NUMBER**

**7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)**
Virginia Commonwealth University
Richmond, VA 23284

**8. PERFORMING ORGANIZATION REPORT NUMBER**

**9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)**
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

**10. SPONSOR/MONITOR'S ACRONYM(S)**

**11. SPONSOR/MONITOR'S REPORT NUMBER(S)**

**12. DISTRIBUTION / AVAILABILITY STATEMENT**
Approved for Public Release; Distribution Unlimited

**13. SUPPLEMENTARY NOTES**

**14. ABSTRACT**

The purpose of the award was to provide funding for the development of a multimodality prostate cancer clinical trial. A clinical protocol was developed along with a supporting infrastructure to begin the trial. A submission to for funding under the DOD Prostate Cancer Clinical Trial Award mechanism; however the project was not funded.

Submission under an alternative funding mechanism is pending collection of more preliminary data and optimization of C-11 acetate synthesis method.

**15. SUBJECT TERMS**
Prostate Cancer, PET, MR, Radiation Therapy

| 16. SECURITY CLASSIFICATION OF: | | | 17. LIMITATION OF ABSTRACT | 18. NUMBER OF PAGES | 19a. NAME OF RESPONSIBLE PERSON |
|---|---|---|---|---|---|
| a. REPORT | b. ABSTRACT | c. THIS PAGE | | | USAMRMC |
| U | U | U | UU | 5 | 19b. TELEPHONE NUMBER *(include area code)* |

## Table of Contents

Introduction:
The following is an itemized list corresponding to the proposed statement of work. The scope of the award was to provide funding for the development of a clinical protocol.

**Key Research Accomplishments**

*A. Development of clinical protocol; Status: Completed.* A full clinical protocol was developed. Investigators adapted the existing imaging and radiation therapy protocols, and developed both a patient management schema and a data management plan. The protocol will include primary source documents and case report forms, informed consent documents, statistical analysis of primary and secondary endpoints, and a proposed budget.

The protocol will provide molecular targeting of prostate cancer within the prostate and the lymphatics. Patients were scheduled to undergo HDR brachytherapy and IMRT, as currently being performed in a Phase I/II Trial at VCU MCC; however, increased dosage would be escalated to sub-volumes with identified disease.

The protocol targeted regions for treatment based upon ultrasmall superparamagnetic iron oxide particle (USPIO), magnetic resonance (MR), and MR spectroscopy imaging (MRSI), but will also develop correlative data using whole body C-11 acetate (AC) PET and USPIO MR imaging of the prostate. The evaluation of the resultant radiation treatment plan (RTP) of either agent may reveal that a single modality can provide similar results. Alternatively, if more extensive disease is indicated by AC PET or USPIO prostate imaging, further validation studies would be indicated to evaluate which modality would be superior for disease identification. The proposal produces clinical data relevant to treatment tolerance and effectiveness, and provides important validation for the application of new imaging technologies.

*B. Integrate preliminary results from ongoing studies into clinical protocol*; **Status: Ongoing.** Practical experience from the current MRSI/brachytherapy program, ongoing Phase I/II IMRT/HDR prostate study, and upcoming USPIO MR breast-imaging study was integrated into the protocol. The AC PET imaging protocol has not yet begun as further optimization of the synthesis methods is being performed.

*C. Development of patient recruitment strategies; Status: Pending Funding of Clinical Protocol.* To ensure rapid accrual of patients, proposed recruitment strategies include development of a patient information website and incorporation of this protocol into existing MCC recruitment programs. Institutional support for the protocol was obtained, and presentation of preliminary data (from independent ongoing VCUMC trials) to a large local private practice urology group was made.

*D. Obtain VCU Radiation Safety, Massey Cancer Center (MCC), Protocol Review and Monitoring System (PRMS), and VCU Institutional Review Board (IRB) approval; Status:.* Radiation safety application and preliminary approval from the MCC PRMS were obtained. Final IRB and IND submissions were not made as funding was not for the performance of the protocol and was not yet secured. The decision was made to optimize the synthetic method of AC prior to IND/IRB submission. Additionally, to

enhance competitiveness of future grant application, further VCU USPIO MR data will be collected and included in the submission.

*E. Validation of image transfer and integration into RTP system.* While single modality imaging data is routinely integrated into the RTP system, a standard operating procedure (SOP) for the transfer and integration of multimodality imaging data is under development to ensure accurate molecular targeting.

A major challenge of this study is to enable the routine conversion of multiple imaging modalities (MRSI-using rectal probe), USPIO MR, AC PET/CT, and transrectal ultrasound (TRUS-used to guide brachytherapy catheter insertion) to a common image format. This is critical to allow rigid registration and segmenting, or thresholding GTV and lymph node target volumes in a consistent format for treatment planning. While all imaging equipment supports DICOM image transfer formats, vendor- and modality-specific differences in format implementation invariably require image and header editing. To this end, Radiation Oncology's MATLAB-based DICOM conversion program will be used to reorder and select images for planning, to repair incomplete header files, to rescale image intensity to accommodate various radiotherapy planning (RTP) systems, and to autocontour structures (e.g., skin surfaces) to facilitate image fusion. The direct incorporation of the TRUS data into the HDR planning system is a complex task and requires further work.

*F. Development of clinical and imaging parameter databases.* A preliminary custom database for archiving clinical and imaging parameter (secondary analysis) data will be developed to enable secure and accurate retrieval of study data.

*G. Apply for physician-sponsored IND for imaging agents.* As described above, NCI will hold an imaging IND for the USPIO MR and AC PET imaging agents. Because a specific protocol is required in an IND submission, we will cross file physician-sponsored INDs for AC and the USPIO agents once the protocol receives IRB approval. As it has been decided, to optimize the AC synthesis method prior to beginning the NCI sponsored AC protocol and funding was not secured for the current study, an IND using the current synthetic method was not yet made.

Concerns in protocol review: A large detractor for the protocol submitted was attributable to "ethical issues"--from the summary statement:
"Serious ethical issues were raised about reimbursement issues and exclusion of patients on ability to pay, and these issues could alter an otherwise attractive study group of African Americans."

It is concerning to us that the assumption was made that those who would be unable to pay for IMRT (i.e., uninsured who DO NOT qualify for Medicare/Medicaid or other financial assistance) will be African Americans. While it would not be possible for this funding mechanism to support IMRT therapy (which is not necessarily standard of care) for those without private or other financial assistance, it is unlikely that this exclusion would alter the recruitment diversity.